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Brief Clinical Report

Thomas Syndrome: Potter Sequence With Cleft Lip/Palate and Cardiac Anomalies

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Holzgreve et al. [Am J Med Genet 18:177–184, 1984] first reported on a syndrome including renal anomalies, heart defect, polydactyly, and cleft palate with other oropharyngeal anomalies. We report here on four sibs with renal adysplasia associated in two with cardiovascular malformations and cleft lip or cleft palate in two. We propose that these patients as the two siblings reported by Thomas et al. [Am J Med Genet 45:767–769, 1993] are affected with a syndrome different of the one described by Holzgreve et al. [Am J Med Genet 18:177–184, 1984] mainly because of the absence of polydactyly. Thomas syndrome is probably inherited as an autosomal recessive trait with marked variability.

KEY WORDS: cleft lip/palate, heart malformations, syndrome, Potter sequence, Thomas syndrome

INTRODUCTION

Potter [1946] originally described the association of bilateral renal agenesis with oligohydramnios and compression deformities of the face and the limbs together with pulmonary hypoplasia. Potter sequence is known to be causally heterogeneous and pathogenetically variable. While most cases are nonsyndromic some are of syndromal origin, chromosomal, monogenic, teratogenic, disruptive, or unknown cause.

We report here on a family in which four patients had a syndrome with Potter sequence and, in some patients, cleft lip/palate and cardiac malformations.

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THE FAMILY

The parents are healthy unrelated Jews of Ashkenazi origin and have three normal living children. The mother had nine pregnancies, the second and fourth ended in an early spontaneous abortion. At the beginning of the 9th pregnancy, the mother was 34 years old and the father was 40 years old. Both had an ultrasound examination of the kidneys which was normal.

Patient 1

During the third pregnancy IUGR was diagnosed and the mother was hospitalised. A girl was born preterm (1,535 g at 36 weeks) and some minor anomalies were noted, in particular a relatively prominent occiput, skin tag on the anterior part of the left ear, very high unusual palate, micrognathia, clenched hands, and rocker bottom feet. Chromosomes were normal (46,XX). She had severe respiratory problems with recurrent pneumothorax and was on a respirator almost all her life. Another major problem which was discovered soon after birth was progressive renal failure. Ultrasound study showed a normal right kidney while the left kidney was not seen. The child also had a large PDA and died at the age of 2 weeks. Autopsy was not done.

Patient 2

Cordocentesis was done on the 20th week of the 7th pregnancy because of oligohydramnios and IUGR; a normal male karyotype 46,XY was found. A boy was born preterm (1,630 g at 36 weeks); he soon developed severe respiratory distress because of hypoplastic lungs. On examination some anomalies were noted including downward slant, beaked nose, simple ears, micropenis, and hypospadias. On ultrasound examination a periventricular cyst was seen in the brain and only one kidney was present. The child died at 1 week and on the biopsy of the single kidney done after death numerous small cysts were seen.

Patient 3

This female fetus died in utero and the 8th pregnancy was interrupted in the 5th month. Pathological study of

TABLE I. Potter Sequence With Cleft Lip/Palate (CL/P) and Cardiac Malformations: The Holzgreve and Thomas Syndromes

Author		Pregnancy	Kidneys	Cleft lip/palate	Cardiac	Other
Holzgreve syndrome						
Holzgreve et al. [1984]		IUGR	Bilateral agenesis	CP, adherent tongue	VSD, Hypoplastic left heart, atresia of aortic arch	Hexadactyly, vertebral abnormalities, 11 ribs
Bonnet et al. [1987]			Hypoplasia	CP	AV canal, dextroposition of the aorta, aberrant right subclavian artery	Polydactyly
Legius et al. [1988]		IUGR	Hypoplasia	CP, bucopharyngeal membrane	Common atrium and AV canal, bicuspid aortic valve	Polydactyly
Thomas syndrome						
Curry et al. [1984]	1	?	Cystic dysplasia	CP	VSD	Toe syndactyly 2–4
	2	?	Cystic dysplasia	CP	Coarctation aorta, aortic valve atresia	
Thomas et al. [1993]	1	Normal	Small	None	Small left atrium, mitral atresia, aortic atresia, Hypoplasia of ascending aorta	
	2	TAB	bilateral agenesis	Bilateral	Complex defect	
Zlotogora et al.	1	IUGR	Absent, nonfunctional	None		
	2	IUGR	Absent, cystic	None	Large PDA	Periventricular cyst; hypospadias
	3	IUFD	Hypoplasia	CL, CP		
	4	Normal, TAB	Agenesis	CP	Tetralogy of Fallot, biscupid pulmonary valve	

IUGR, intrauterine growth retardation; IUFD, intrauterine fetal death; CP, cleft palate; CL, cleft lip.

the macerated fetus showed posterior cleft palate and a small cleft of the lip and bilateral hypoplastic kidneys.

Patient 4

At the 16th week of the 9th pregnancy ultrasound examination demonstrated severe oligohydramnios and absent kidneys; therefore the pregnancy was interrupted. The male fetus was macerated; its measurements were compatible with gestational age. Pathological examination confirmed bilateral renal agenesis and diagnosed a severe congenital heart malformation including tetralogy of Fallot and bicuspid pulmonary valve. The fetus also had low-set posteriorly angulated ears and hypertelorism as well as a severe micrognathia. The tongue was short and a cleft of the hard and soft palate was noted.

DISCUSSION

Potter sequence is often associated with other malformations such as cardiac malformations or cleft lip/palate. In the original series of 50 patients with renal agenesis reported by Potter [1965], 11 had a heart malformation and 3 had cleft lip/palate; however, she did not distinguish between patients in which the sequence was the part of a syndrome and those in which it was not. Among 62 patients with nonsyndromal Potter sequence reported by Curry et al. [1984], cardiac defects were present in 6 while cleft lip/palate was not mentioned. In the same report among the patients with multiple congenital anomalies, in 2 Potter sequence was associated with heart malformation and cleft lip/palate [Curry et al., 1984]. In 1984 Holzgreve et al. reported on a fetus with Potter sequence, heart defect, polydactyly, and cleft palate together with additional malformations in particular adhesion of the tongue to the posterior cleft palate and skeletal defects. Subsequently, Bonnet et al. [1987] and Leguis et al. [1988] each reported an isolated patient with the similar combination of Potter sequence, heart defect, polydactyly, and cleft palate. The patient reported by Leguis et al. [1988] had also an intrabuccal band. When Thomas et al. [1993] reported on two sibs, one with hypoplastic left heart sequence and small kidneys and the other with bilateral cleft lip and palate, complex heart defect, and bilateral renal agenesis, they considered these cases to represent the first familial examples of the Holzgreve syndrome. The patients described in the present report are very similar to those reported by Thomas et al. [1993]: the three major malformations were present in one of our patients while the other three patients had a milder form of the Potter sequence with some of the other traits of the syndrome. Our four patients and the two sibs reported by Thomas et al. [1993] did not have polydactyly, intrabuccal bands, and/or other malformations as the original patients with Holzgreve syndrome. We propose therefore to distinguish between two entities: Holzgreve syndrome and Thomas syndrome (Table I). In Thomas syndrome renal adysplasia may be isolated or associated with other malformations such as cardiac defects and/or cleft lip/palate. The two patients reported by Curry et al. [1984] with Potter sequence, cardiac defect, and cleft lip/palate may have had the Thomas syndrome. It may be that Thomas syndrome is relatively frequent since, as seen in the two families with multiple affected children the syndrome is variable and some of the patients presented with only renal adysplasia. In both families in which Thomas syndrome has been reported the kidneys of the parents were examined ultrasonographically and were normal. It may be that the syndrome is inherited as an autosomal recessive trait; however, no conclusions about the inheritance can be made yet.

Renal adysplasia is usually considered to be inherited as an autosomal dominant trait with incomplete penetrance [McPherson et al., 1987]. While some of the families clearly fit to this type of inheritance in some cases more than one sib is affected without any evidence of other affected individuals even after a complete familial investigation [Al Saadi et al., 1984]. While this observation does not rule out dominant inheritance, it may be due to heterogeneity. Some of the patients with renal adysplasia may be affected with a recessive disorder such as the Thomas syndrome.

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